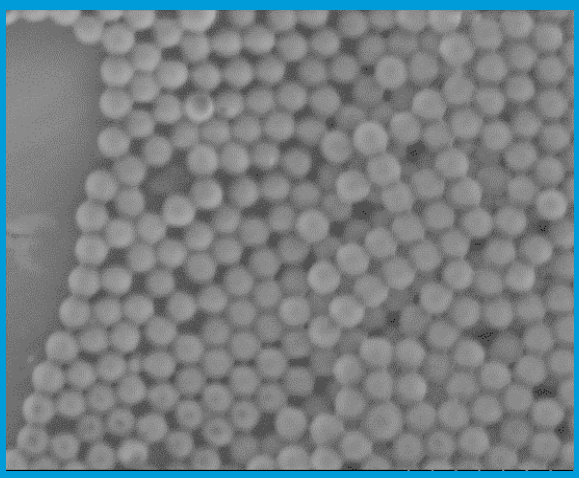
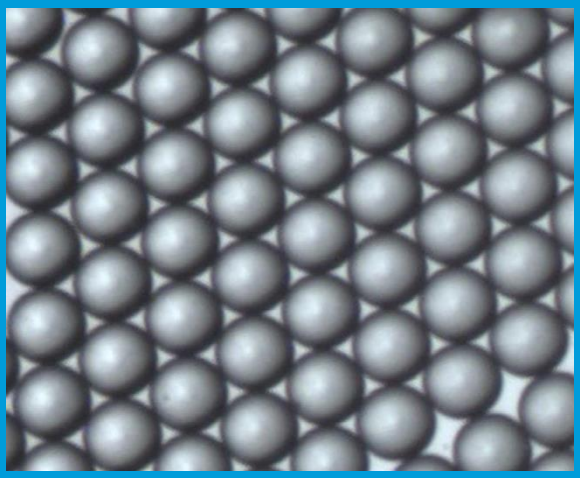
Continuous Synthesis of Monodisperse PLGA Particles using Droplets

Droplet system for controlled and reproducible encapsulation of API in uniform polymer beads





Version 1.2

21/04/2017

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dolomite

Summary

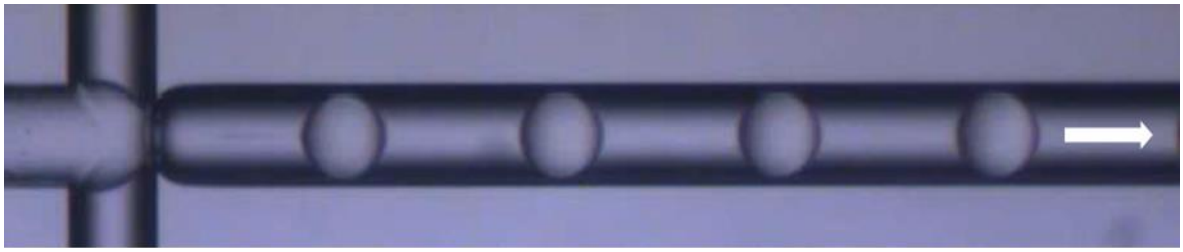
This application note describes methodology for fabrication of highly monodisperse Poly (lactic-co-glycolic acid) (PLGA) beads with sizes ranging from 10 to 45µm using Dolomite's droplet microfluidic system.

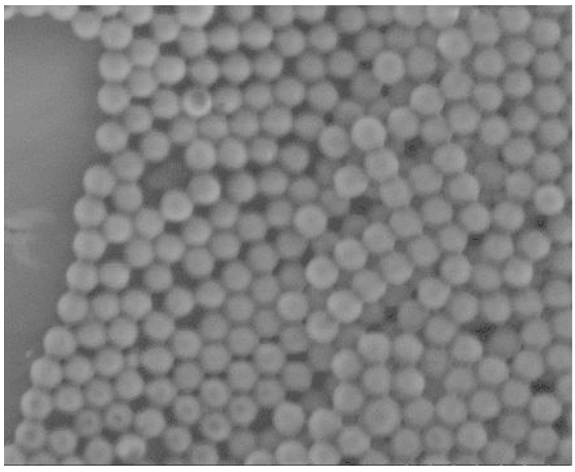
The methodology of bead fabrication described herein relies on dissolution of the polymer in a solvent followed by emulsification using a droplet microfluidic chip. The key advantages of this approach are the high monodispersity and batch-to-batch consistency of the resulting beads. The wide size range achievable on one system without hardware changes is a strong benefit as well.

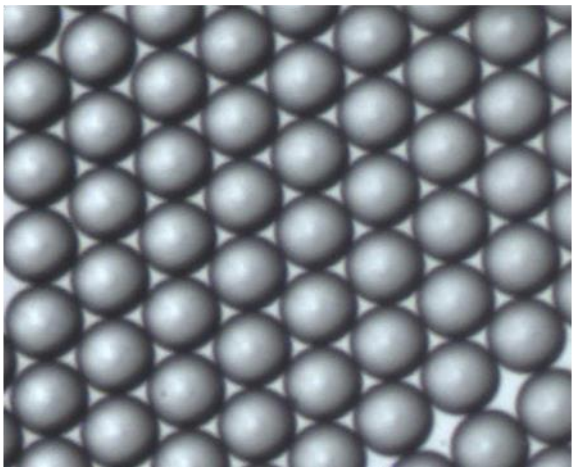
A production setup is recommended with a priming and production protocol. This is operated over a range of test conditions where relative flow conditions are varied between the droplet fluid and the carrier fluid. The resulting droplet sizes and droplet rates are documented. A physical mechanism is illustrated describing the process of collection, and conversion of the droplet from liquid phase to solid phase.

Key parameters achieved during the tests are:

- Droplet flow rate range: 0.5 – 30 µL/min
- Carrier flow rate range: 10 – 125 µL/min
- Droplet size range: 35 – 101 µm
- Particle size range: 12 – 44 µm (2 µm size particles produced in separate tests)
- Maximum droplet rate achieved: 14 kHz
- Polymer concentration used: 1, 2, 10, & 20 % (w/v)
- Highly monodisperse particles (less than 5% cv)





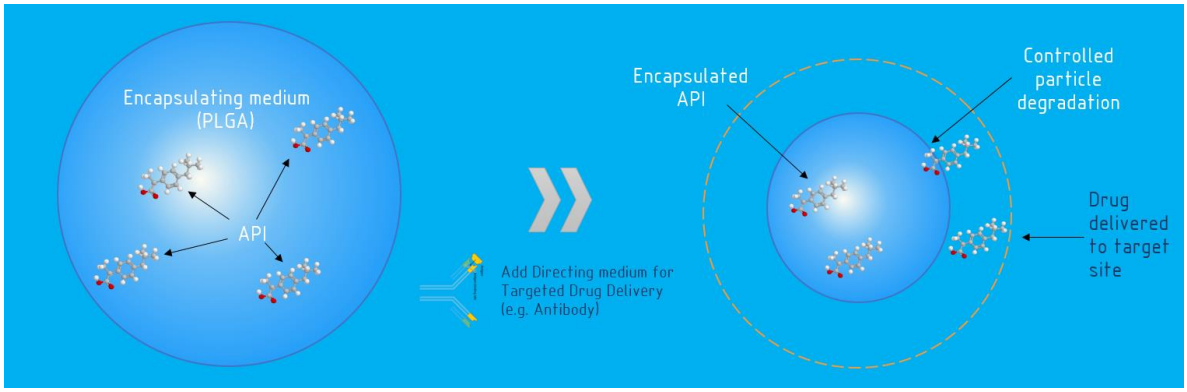


Introduction

Poly(lactic-co-glycolic acid) or PLGA is a polymer that has broad utility as vehicles for drug delivery and form the basis of several therapies approved by the US Food and Drug Administration, owing to its biodegradability and biocompatibility..

There is a recognized need to for fabrication of highly monodisperse beads for applications such as controlled drug release and targeted drug delivery.

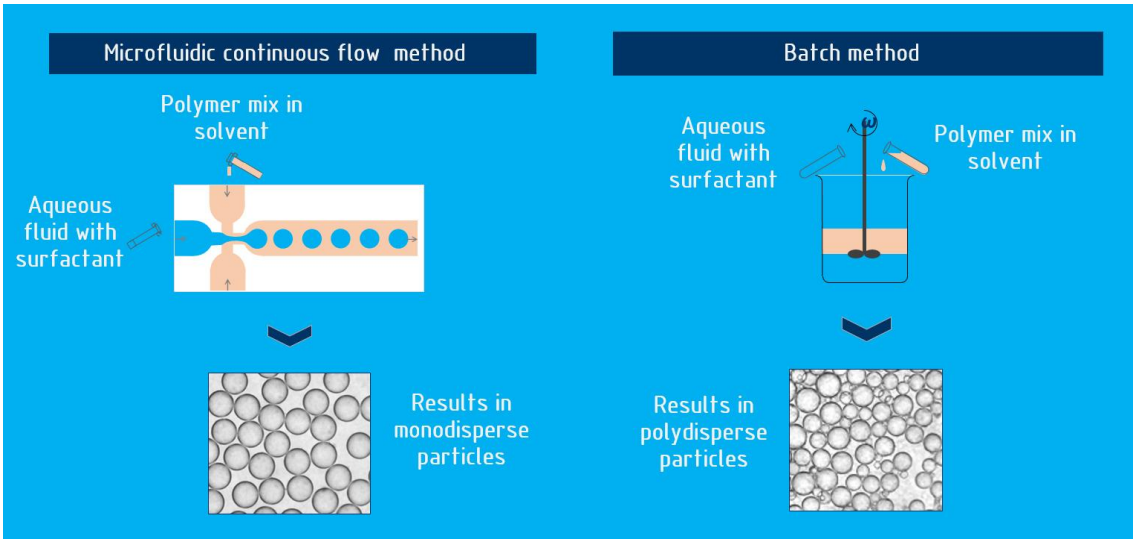
In these applications precision control over the bead size distribution is particularly important as it has a significant effect on preferential segregation within the body (Enhanced Permeability and Retention Effect). Further, bead size determines the degradation rate and consequently the rate of drug release. Bead size has a dramatic effect on the surface area to volume ratio and consequently affects the quantity of the functional coating groups. In targeted drug delivery applications, this in turn determines the preference the beads have for navigation to specific site.



API is released constantly over time thanks to the controlled degradation of the PLGA bead

Conventional emulsion-based methods of manufacturing PLGA particles produce beads with a wide range of diameters (and thus properties) in each batch. There is limited degree of size selection by controlling the shear energy input.

The flow based microfluidic method demonstrated here yield highly monodisperse particles in a single step, thereby increasing the yield of the process.

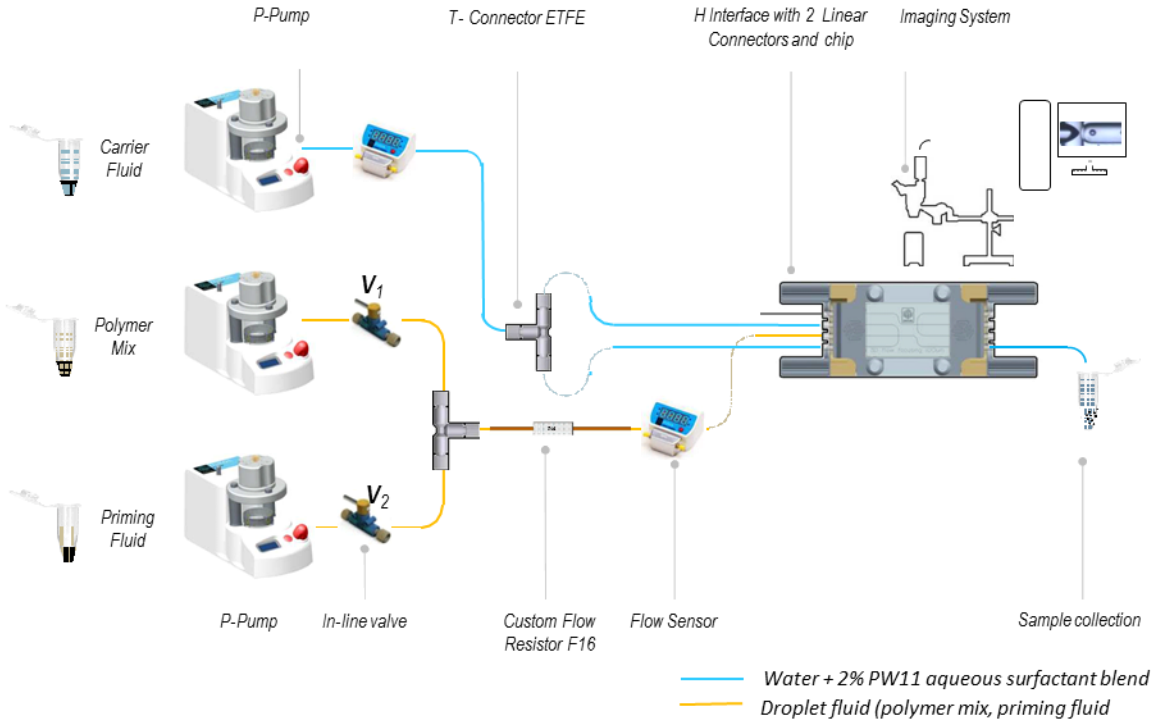


Materials and methods

PLGA beads production using the microfluidic method is achieved by formation of droplets followed by solvent extraction. Two partially miscible solvents dichloromethane (DCM) and water are used. PLGA is dissolved in DCM and forms the droplets fluid. Aqueous surfactant blend forms the continuous phase fluid. The surfactant adsorbs to the fluid interface between the droplet and carrier, and stabilizes the emulsion.

1. Setup overview

The system was set-up with 3 Mitos P-Pumps (Dolomite part number: 3200016) and in-line Mitos Flow Rate Sensors (Dolomite part numbers: 3200097 and 3200098) to monitor the flow rates. A calibration was carried out to give accurate flow rate readings for the droplet phase (see Appendix A). A helium gas supply up to 10 bar was connected to the P- Pumps. This along with flow resistance of the system prevented outgassing of the DCM- PLGA solution. Outgassing leads to uncontrolled precipitation of polymer in the system which creates flow instabilities (and blockages in some extreme cases)



Schematic of the microfluidic setup used to make PLGA beads.

The organic flow line sensor is connected to the pump containing the polymer mix to enable flow control mode of operation during production. The priming is done in pressure-control mode.

2. Microfluidic Chip

A 3D flow focussing droplet chip 100µm hydrophilic (Dolomite part number: 3200433) is used to create droplets. The 3D flow focussing design minimises fouling of the channel walls after the junction and enable mulit-hours operation of the chip without risk of blockage. This is due to the particular 'pore' structure on the outlet side of the droplet forming junction which creates a 3D

sheath flow in the droplet pinch-off region. This flow pattern is especially useful when handling droplet fluids which are liable to foul the junction surface.

The 3D flow focussing chip is installed in a Chip interface H (Dolomite part number: 3000155). Two 4-way edge connectors (Dolomite part number: 3000024) help create a leak proof seal between tubing and the chip. A software controlled high speed imaging system (Dolomite part number: 3200050) focussed at the junction of the microfluidic chip enables visualization.

3. Tubing Setup

Aqueous carrier line

Section	FEP Tubing OD(mm), ID(mm); L(mm)
Compressor to P-Pump	Pneumatic (provided with P-Pump)
Pump to Flow sensor adaptor	1.60, 0.25, 300
Flow sensor adaptor to sensor (3200097)	0.80, 0.40, 300 (provided with sensor)
Sensor to Flow sensor adaptor	0.80, 0.40, 300 (provided with sensor)
Flow sensor adaptor to 2-way in line valve	1.60, 0.25, 500
2-way in line valve to T-connector ETFE	1.60, 0.25, 200
T-connector ETFE to Chip	2 × (1.60, 0.10, 300)

Organic droplet line

Section	FEP Tubing OD(mm), ID(mm); L(mm)
Compressor to P-Pump	Pneumatic (provided with P-Pump)
Pump to 2-way in line valve	1.60, 0.25, 300
2-way in line valve to T-connector ETFE	1.60, 0.25, 500

Organic priming line

Section	FEP Tubing OD(mm), ID(mm); L(mm)
Compressor to P-Pump	Pneumatic (provided with P-Pump)
Pump to 2-way in line valve	1.60, 0.25, 300
2-way in line valve to T-connector ETFE	1.60, 0.25, 500

Combined droplet and priming line

Section	FEP Tubing OD(mm), ID(mm); L(mm)
T-connector ETFE to Flow sensor adaptor	0.80, 0.40, 300 (provided with sensor)
Sensor to Flow sensor adaptor	0.80, 0.40, 300 (provided with sensor)

Flow sensor adaptor to chip	1.60, 0.10, 900

Collection line

Section	FEP Tubing OD(mm), ID(mm); L(mm)
Chip to collection	1.60, 0.25, 300

4. Reagents

The three pumps are loaded with droplet fluid, priming fluid, and carrier fluid.

Droplet fluid	Dichloromethane + PLGA
Priming fluid	Dichloromethane
Carrier fluid	Water + 2% PW11 aqueous surfactant blend

- Priming fluid: Dichloromethane (DCM) was passed through a 0.2 µm pore filter and used without further modification.
- Droplet fluid preparation: PLGA was dissolved in DCM at room temperature by stirring over the course of an hour. 10 ml volumes of 4 concentrations were prepared – 1, 2, 10, and 20% (w/v).
- Carrier fluid: 2% PW11 surfactant blend was passed through a 0.2 µm pore filter and used without further modification.

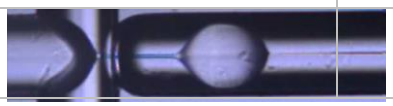
Reagent	Supplier	Part Number
Poly(D,L-lactide-co-glycolide) – ester terminated, lactide:glycolide 75:25, Mw 76,000-115,000	Sigma Aldrich	719927
Dichloromethane – CHROMASOLV®, for HPLC, ≥99.8%, contains amylene as stabilizer	Sigma Aldrich	34856
2% PW11 surfactant blend	Particle Works	7206001

There are two valves on the pump lines – the priming fluid valve *V2* and the droplet fluid valve *V1*. The use of two valves allows priming the system (see Appendix C), and then bringing in the droplet fluid without fluidic interruption on-chip. This also enables the continuous phase flow to be started first before opening the valve to start the droplet flow.

Results

After droplet formation, DCM begins to diffuse into the surrounding aqueous phase (DCM has a 2% (v/v) solubility in water at room temperature) thereby depleting the droplets of solvent. The solvent depletion from the droplet increases PLGA concentration until supersaturation is reached and therefore PLGA particles precipitate. This diffusive release of solvent continues as there is sufficient fresh water available close to each droplet. Eventually, as most of the solvent is removed from the droplet solid content remains. At this stage, the droplet is converted to a PLGA bead. The removal of the solvent causes a proportional reduction in volume, and therefore size. Thus, the droplets visibly shrink in size.

To demonstrate the workflow of estimating size changes, a sample is collected using test conditions in the below table.

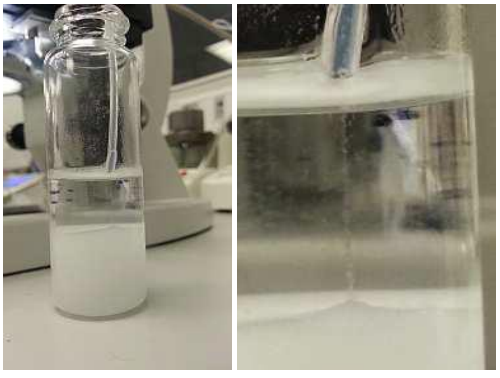
Carrier		Droplet		Junction Image	Droplet Diameter	Droplet Rate
Pressure/ mbar	Flow rate µL/mi	Pressure/mbar	Flow rate µL/mi		µm	Hz
270	10	202	1.35		101	1

The size of the droplet is measured by using a pixel analysis software. The reference dimension is taken as the channel width of 100 µm. Videos of droplet production are recorded at a frame rate of 1 kHz for a pixel size of 592 px × 144 px using the high-speed imaging system.

Where the droplet production rate is higher than the video capture rate, a still image is recorded. This is found to sufficient to measure the droplet size. Droplet rate is then estimated by

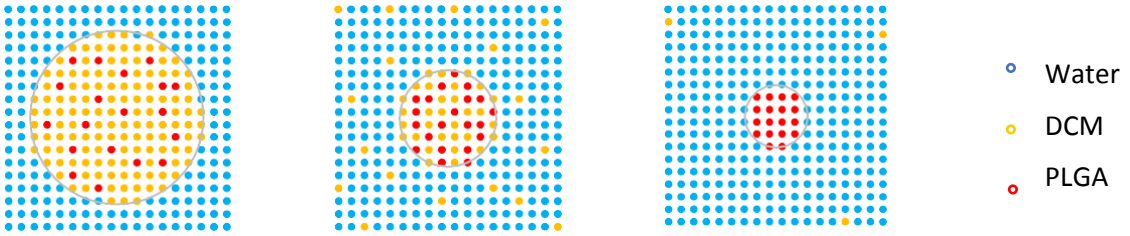
Droplet rate (Hz) = Droplet phase flow rate (µL/s) / Droplet volume (µL)

The droplets made on chip are collected in a vial. The vial is pre-filled with 100 µL of carrier fluid (Water + 2% PW11 aqueous surfactant blend).



Left: Outlet tubing from chip dips into the collection fluid. Right: Droplets exiting tubing, falling through the aqueous phase, and collecting at the bottom of the vial.

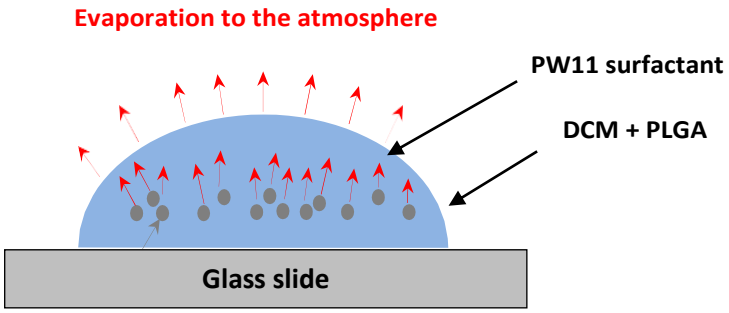
Solvent removal is the diffusive movement of dichloromethane from the droplet, across the droplet/carrier fluid interface, and into the carrier. The dichloromethane is progressively removed from the collected sample, and effused to the atmosphere. Left behind are solidifying PLGA beads suspended in carrier fluid.



Conceptual molecular schematic of solvent removal

In the presence of abundant aqueous fluid, the solvent continuously diffuses out of the droplet. The remnant hydrophobic polymer forms a microparticle of smaller size than the initial droplet. The surfactant molecules (not illustrated above) self-assemble at the fluid interface between the organic droplet and aqueous carrier - the hydrophobic part of the surfactant molecule intrudes into the droplet while the hydrophilic part extends outwards.

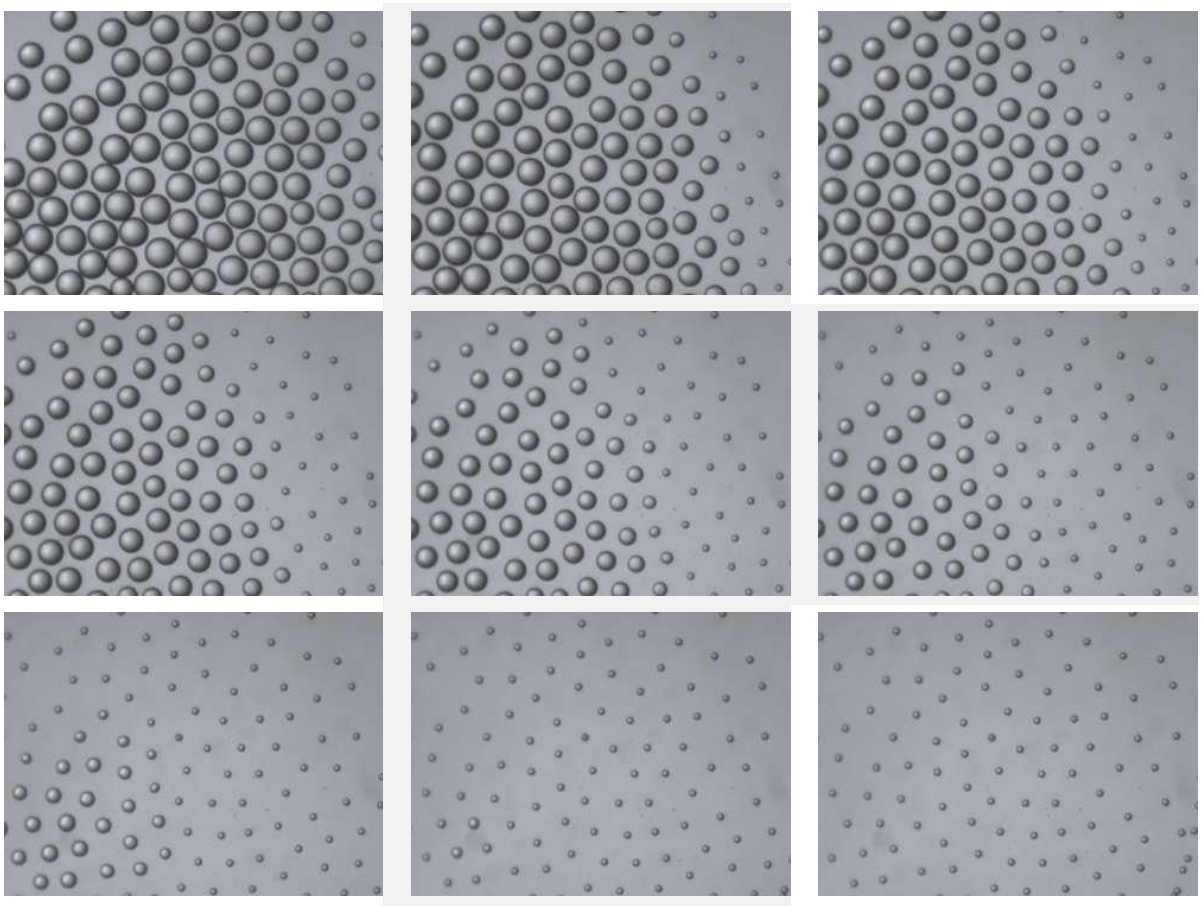
To collect and analyse a small sample, the outlet tubing is removed from the collection vial, and the sample is instead collected on a small glass cover slide. The cover slide is inspected under a microscope, and images are recorded over fixed time intervals.



Arrows indicate transfer route of DCM from the droplets to the water

The polymer droplets settle at the bottom of the water droplet on the glass cover slip. The cover slip is uncoated, and hence hydrophilic, the same surface as the droplet chip. There is sufficient exposed surface area for the DCM to transfer from the polymer droplets to the surrounding water, and eventually diffuse out to the atmosphere.

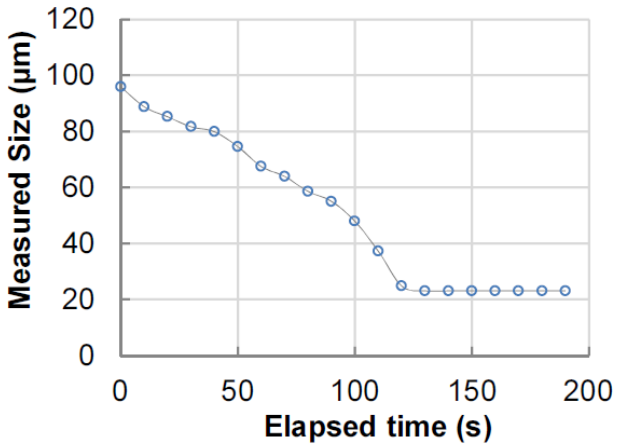
The image sequence below shows the size evolution of the collected sample.



Sequence of images 30 seconds apart. Pixel resolution for size estimation is 1.77 µm/px.

The variability of solvent removal is apparent from the differences between droplets. However, being monodisperse, all droplets have identical initial size and final size.

One droplet/particle is selected, and tracked during the solvent removal process. The sizes are recorded. The particles continue to be surrounded by the carrier phase fluid, and hence in a fluid suspension.

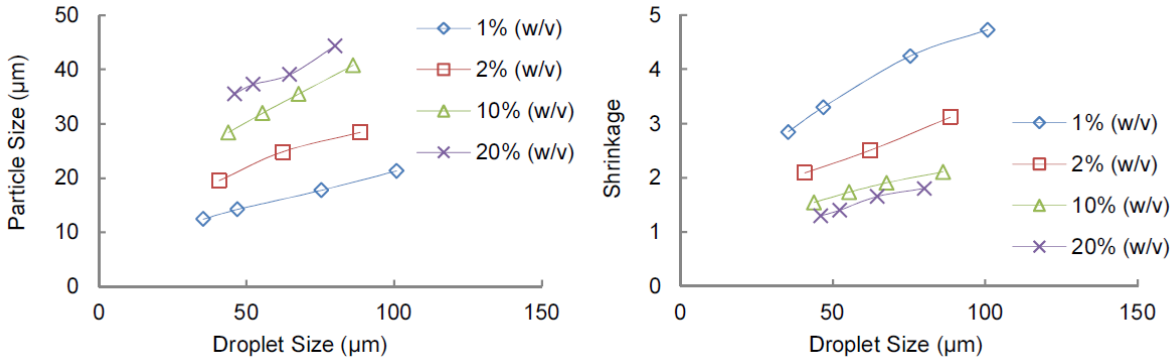


Shrinkage of a tracked droplet

The shrinkage starts as soon as the droplet is formed on the chip. For this reason, by the time the size is tracked under a microscope, the size has reduced from 101 µm to 95 µm. The graph shows the terminal size of the droplet to be 23 µm.

Shrinkage = (Size of droplet) / (Size of particle)

In the above test case, shrinkage is 101 µm/23 µm = 4.36. At the terminal size, the droplet is said to have lost most of the DCM content, leaving behind a semi-gel like PLGA micro particle.



Left: Relationship showing the final particles sizes achieved with starting droplet size for various polymer concentrations. Right: Shrinkage versus starting droplet size for various polymer concentrations.

Droplet sizes and bead sizes

The rate of removal of the solvent is strongly tied with the strategy of removal. On a cover slip, there is large exposed surface area for evaporation, and therefore solvent removal progresses to completion in a few minutes. In column method, solvent exchange, the solvent removal may take longer yet be more controlled.

The droplet sizes vary as a function of the flow ratio (flow rate of droplet fluid/flow rate of carrier fluid). Full list of results and picture of droplets can be found in Appendix D. The pinch off of the droplets depends on various physical parameters such as flow ratio, interfacial surface tension, and fluid viscosities. The droplets were produced on-chip, and transport off-chip for conversion from liquid phase to solid phase. The surfactant adequately stabilized the emulsion during this conversion phase.

	Droplet size/Bead size (smallest)		Droplet size/Bead size (largest)	
Polymer concentration	Droplet size	Bead size	Droplet size	Bead size
1% (w/v)	35 µm	12 µm	101 µm	23 µm
2% (w/v)	26 µm	16 µm	88 µm	28 µm

10% (w/v)	44 µm	28 µm	86 µm	40 µm
20% (w/v)	46 µm	35 µm	80 µm	44 µm

Droplet Production Rate

Polymer concentration	Maximum droplet rate
1% (w/v)	14,007 Hz
2% (w/v)	10,996 Hz
10% (w/v)	2,832 Hz
20% (w/v)	471 Hz

Conclusion

Droplet microfluidics has been demonstrated to be a very effective tool for production of PLGA beads with high monodispersity and size homogeneity.

Microfluidics allow seamless control of the size of the beads by varying the flow rates of carrier and droplet phases, as well as changing the concentration of the PLGA in the droplet phase. In this work, bead sizes ranging from 12µm to 44µm have been obtained on the same microfluidic system with no change in hardware.

Optical microscopy of samples obtained within this study has demonstrated extremely high bead uniformity, which in turn results in a homogenous degradation and drug release.

Options for scaling-up the production of PLGA beads and increase the throughput are available, notable Dolomite Telos multi-channel platform.

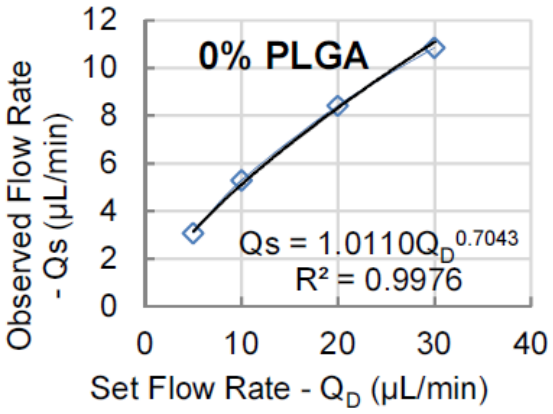
Appendix A: System Component List

Part No.	Part Description	#
3200016	Mitos P-Pump	3
3200095	Mitos Sensor Display	2
3200097	Flow Rate Sensor 30 - 1000µl/min	1
3200098	Flow Rate Sensor 1 - 50 µl/min	1
3200117 OR 3200118	Mitos Compressor 6bar (230V/50Hz) OR Mitos Compressor 6Bar (110V 60Hz)	1
3200050	High Speed Imaging System	1
3000024	4-Way edge Connector	2
3000155	Chip interface H	1
3200310	Microscope Stage Adaptor Kit for Edge Interfaces	1
3200063	FEP Tubing 1/16" x 0.25mm x 10m	1
3200300	FEP Tubing, 1/16" x 0.1mm, 10 metres	1
3000397	T-Connector, ETFE	1
3200049	Custom Flow Resistor Kit	1
3200087	2-way In-line Valve	2
3000477	Pack of 10 ETFE fittings and ferrules	1

Appendix B: Flow rate calibration for Dichloromethane

0% PLGA

A calibrated positive displacement pump was used to pump the DCM solution at reference flow rate Q_D. The observed and uncalibrated flow rate read by the flow sensor (set to water as the working fluid) is Q_S. Plotting the two results in the calibration curve.



Calibration curve for 0% PLGA solution

Inverting the trendline equation gives

$$\mathbf{Q_D = (Q_s/1.011)^{(1/0.7043)}}$$

During tests, the P-Pumps were run in flow control mode, and the calibration fluid set to water. The actual flow rates were determined by the calibration done *a priori*.

Flow rate on P-Pump via FCC (Q_S)	Actual flow rate through chip (Q_D)
1.00 µL/min	0.98 µL/min
5.00 µL/min	9.67 µL/min
10.00 µL/min	25.88 µL/min

Appendix C: Priming method

Priming – V1 closed V2 open

In pressure control mode, DCM droplets are established in the carrier fluid. This is a safe start considering that a backflow, jetting, or chaotic flow regime do not cause any irreversible effects (polymer would precipitate and create blockages). The objective is also to purge the fluid pathways of gases, and to condition the chip surface with the surfactant. This is a check to ensure chemical compatibility with all wetted parts in the system. It is advisable to do the priming at reasonably high flow pressure (2-3 bar).

It should be kept in mind that valves should be closed only when pumps are in pressure control mode. When priming fluid droplet production is well established, the valves may be switched so that priming valve V1 is closed, and droplet valve V2 is open. The pump with the droplet fluid is kept at the same pressure as the priming pump. This valve switch will cause the droplet fluid to arrive at the chip. There will be very little visible change when observing droplets via the imaging system. After a few minutes, the polymer mix arrives at the chip, and starts producing polymer particles.

After a few minutes more, both pumps were then switched to flow control mode.

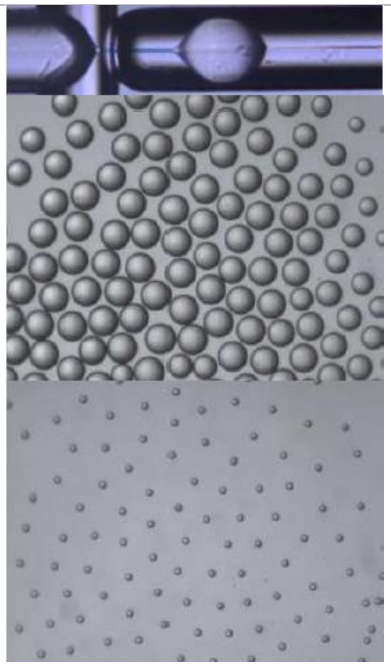
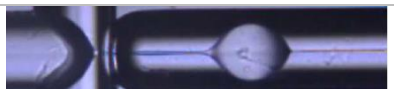
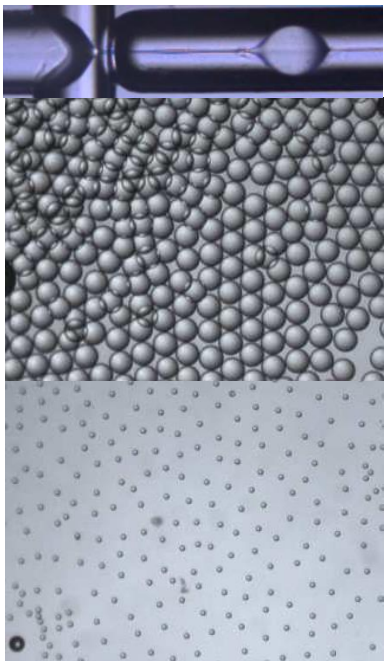
Shutdown at the end of the production run follows the reverse routine followed for priming. The pumps are switched to pressure-control mode. The valves are switched to change the flow from droplet to priming fluid. The system is allowed to cleanse out for about 10-15 minutes.

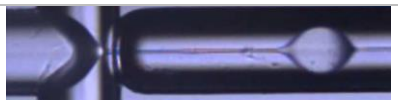
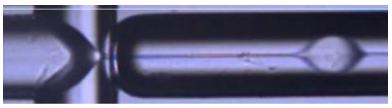
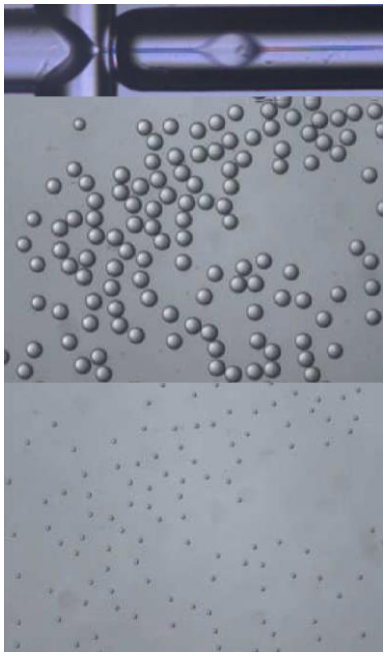
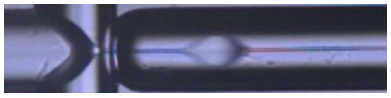
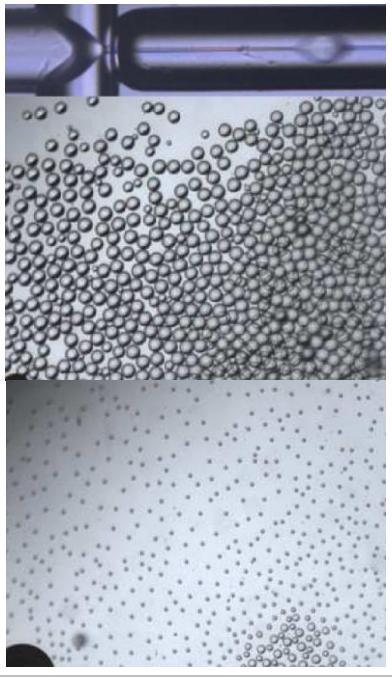
- When operating in pressure control mode, the temperature of the fluid is important in maintaining constant flow rate. For long duration running, it may be beneficial to use hotplates to control the temperature of the input liquids, as changes in temperature lead to a change in viscosity causing a drift in flow rate.
- Flow control mode is helpful for long duration running in making small adjustments to the pressure to maintain constant flow rate. However, significant blockages in the system cannot be compensated using this method.

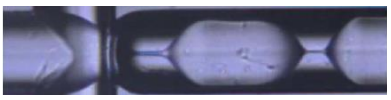
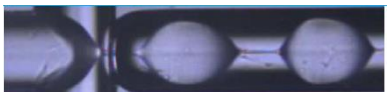
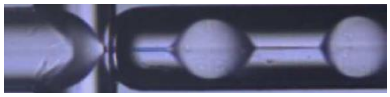
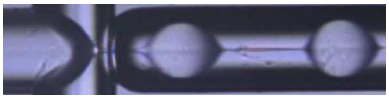
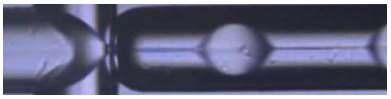
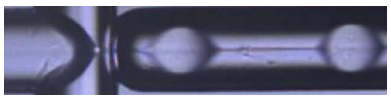
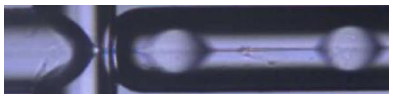
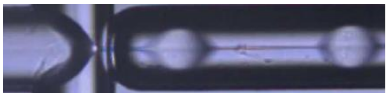
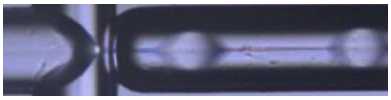
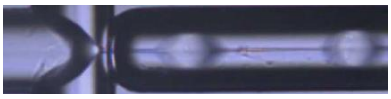
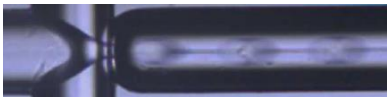
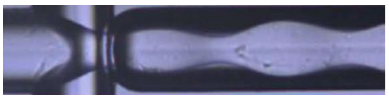
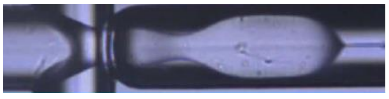
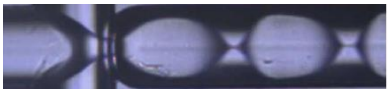
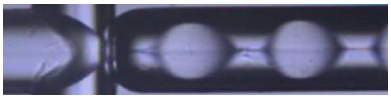
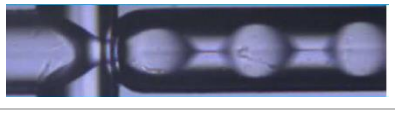
Appendix D: Droplet Diameters and Rates

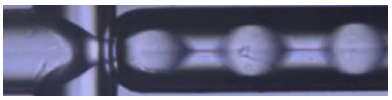
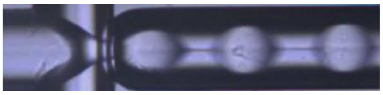
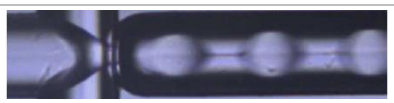
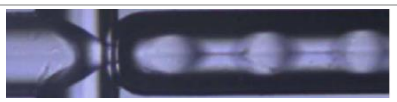
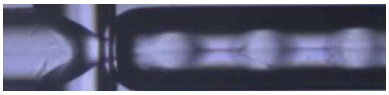
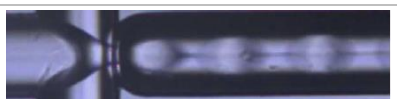
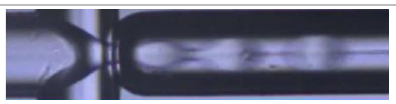
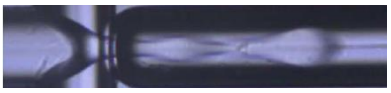
The following table shows droplet size and rates for many different test conditions. Each test condition differs in the set flow rate on the two fluid lines.

1.1.1 1% PLGA solution

Carrier		Droplet		Junction Image	Droplet Diameter	Droplet Rate
Pressure/ mbar	Flow rate µL/min	Pressure/ mbar	Flow rate µL/min		µm	Hz
270	10	202	1.35		101 (on chip) 95 (initial size on glass slide) 23 (final size on the glass slide)	1
520	20	199	1.35		88	64
804	30	221	1.35		75 (on chip) 73 (Initial size on glass slide) 17 (final size on glass slide)	100

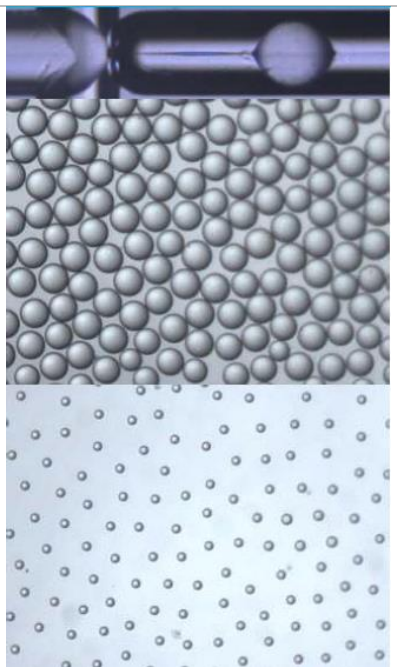
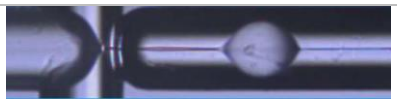
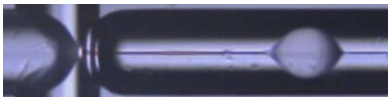
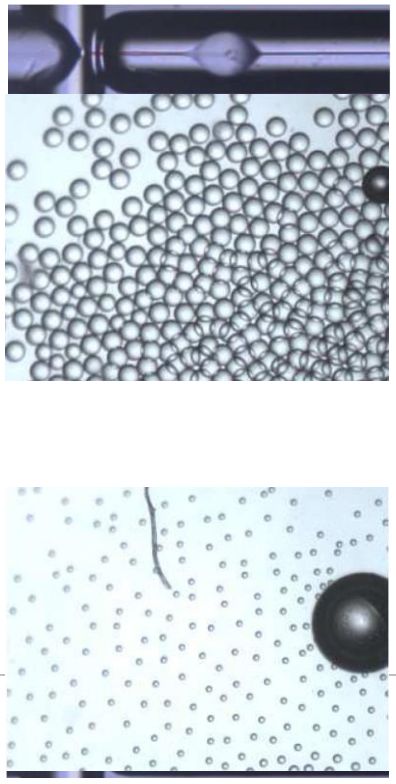
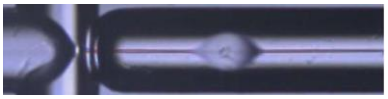
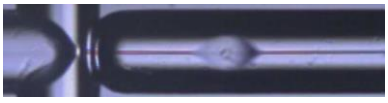
1125	40	243	1.35		68	138
1432	50	266	1.35		60	198
1732	60	288	1.35		53	287
2032	70	310	1.35		47 (on chip) 43 (Initial size) 14 (final size)	415
2333	80	331	1.35		42	598
2622	90	354	1.35		38	800
2910	100	375	1.35		35 (on chip) 33 (initial size on glass slide) 12 (final size on glass slide)	967

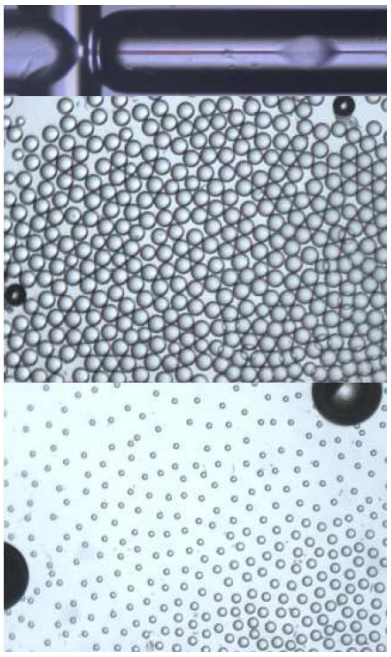
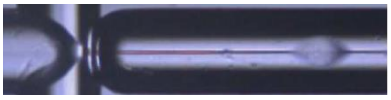
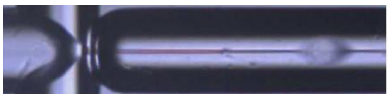
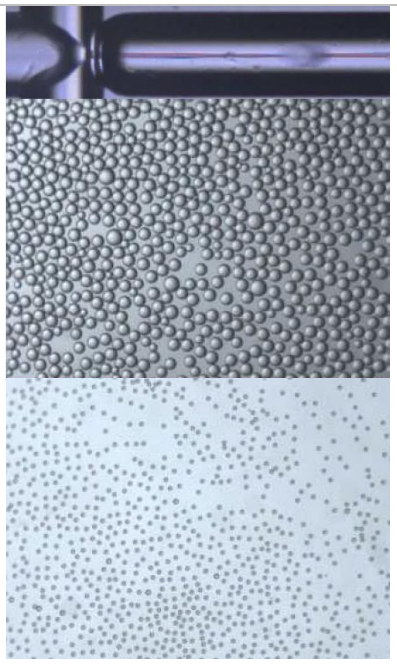
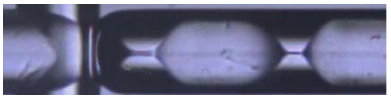
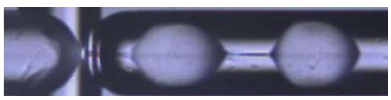
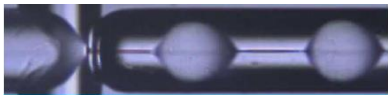
400	10	819	12.21		-	-
670	20	836	12.21		96	437
909	30	806	12.21		83	678
1190	40	804	12.21		75	935
1482	50	815	12.21		68	1211
1773	60	831	12.21		62	1606
2075	70	851	12.21		55	2287
2363	80	869	12.21		51	2929
2644	90	887	12.21		47	3742
2931	100	906	12.21		42	5130
4449	150	1022	12.21		32	11520
388	10	1823	31.54		-	
769	20	1964	31.54		-	
1079	30	2013	31.54		90	1377
1387	40	2024	31.54		82	1800
1666	50	2011	31.54		76	2287
1925	60	1992	31.54		69	3026

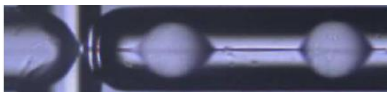
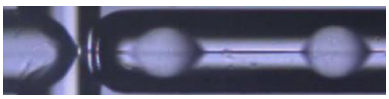
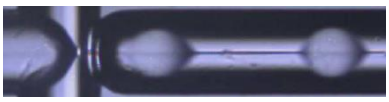
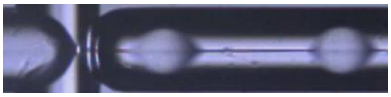
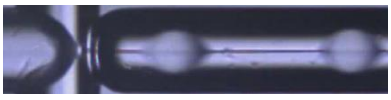
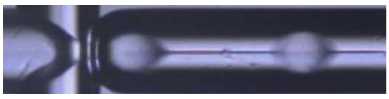
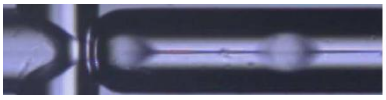
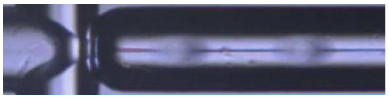
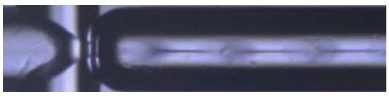
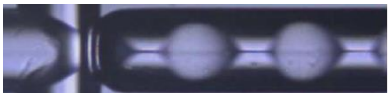
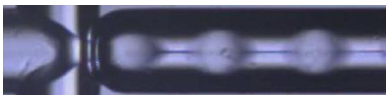
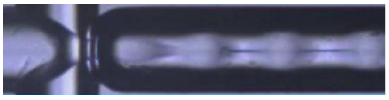
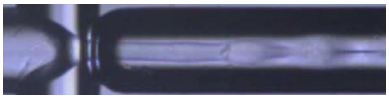
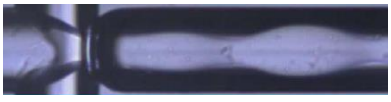
2201	70	1993	31.54		64	3857
2475	80	2002	31.54		60	4648
2745	90	2011	31.54		55	5909
3028	100	2024	31.54		52	7015
3320	110	2038	31.54		48	8821
3607	120	2053	31.54		45	10739
3952	130	2118	31.54		42	14007
4234	140	2131	31.54		Chaotic	-

1.1.2 2% PLGA solution

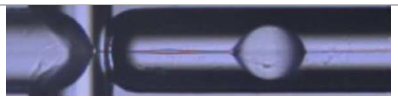
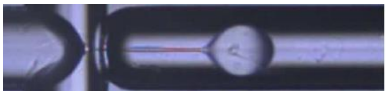
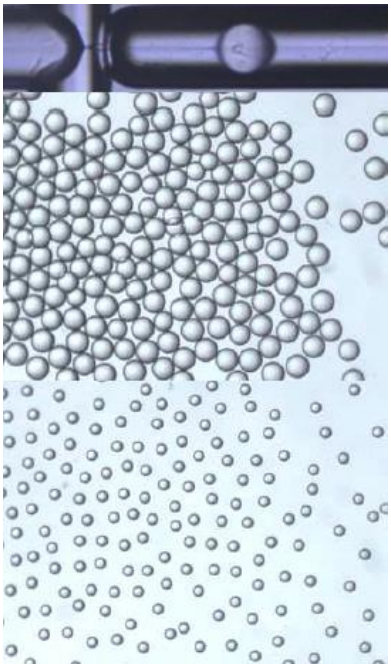
Carrier		Droplet		Junction Image	Droplet Diameter	Droplet Rate
Pressure/ mbar	Flow rate µL/min	Pressure/ mbar	Flow rate µL/min		µm	Hz

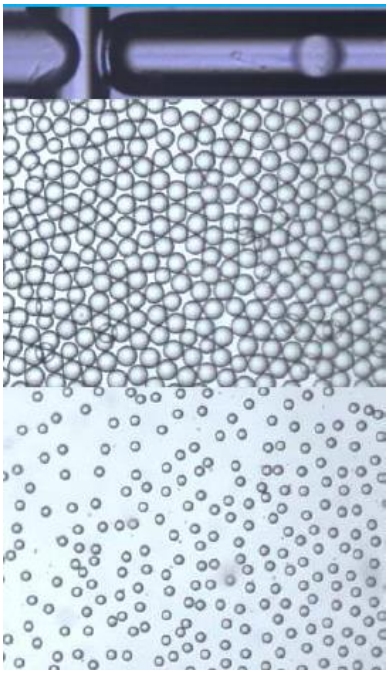
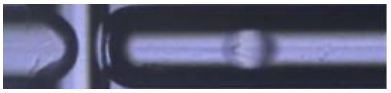
271	10	270	1.17		88 (on chip) 86 (initial size on glass slide) 28 (final size on the glass slide)	54
522	20	278	1.17		77	82
793	30	294	1.17		68	116
1087	40	320	1.17		62 (on chip) 62 (initial size on glass slide) 24 (final size on glass slide)	155
1450	50	341	1.17		56	211
1696	60	361	1.17		49	313
1984	70	383	1.17		44	443

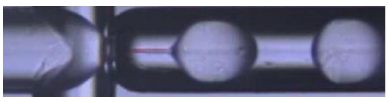
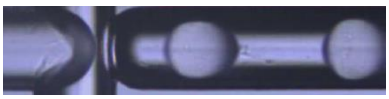
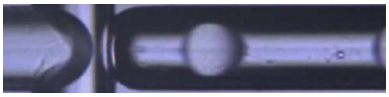
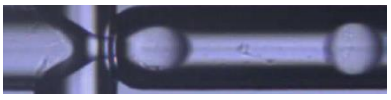
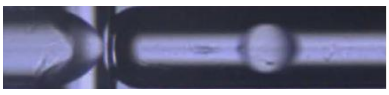
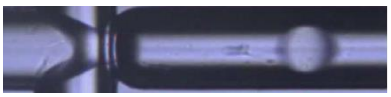
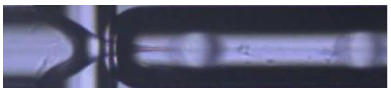
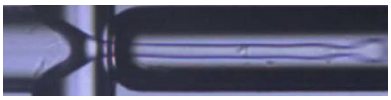
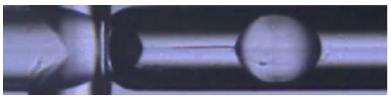
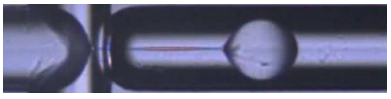
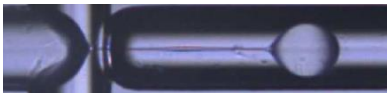
2257	80	402	1.17		41 (on chip) 39 (initial size on glass slide) 19 (final size on glass slide)	552
2533	90	402	1.17		36	791
2824	100	445	1.17		34	964
3534	125	498	1.17		26 (on chip) 23 (initial size on glass slide) 16 (final size on glass slide)	2089
393	10	1160	9.33		-	-
626	20	1176	9.33		89	418
883	30	1160	9.33		83	518

1162	40	1159	9.33		76	672
1450	50	1165	9.33		70	866
1725	60	1179	9.33		62	1227
2007	70	1196	9.33		57	1603
2280	80	1215	9.33		53	1986
2560	90	1234	9.33		48	2737
2829	100	1253	9.33		44	3485
3550	125	1309	9.33		35	6925
4286	150	1368	9.33		30	10996
406	10	2799	22.77		Chaotic	-
1586	50	2948	22.77		80	1416
2931	100	2978	22.77		54	4643
3653	125	3052	22.77		44	8599
4406	150	3089	22.77		Chaotic	-
1732	50	5511	38.38		Chaotic	-
3089	100	5544	38.38		Chaotic	-

1.1.3 10% PLGA solution

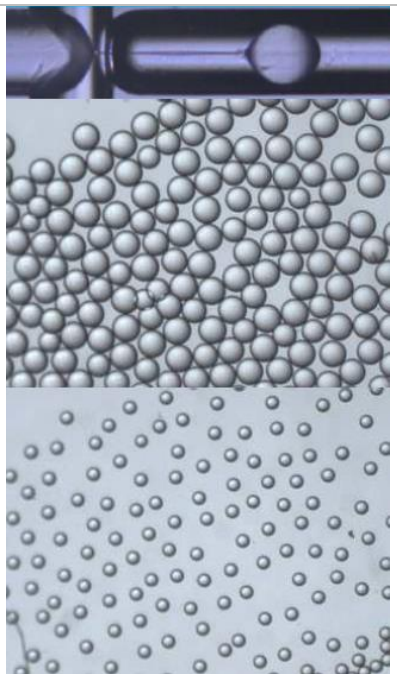
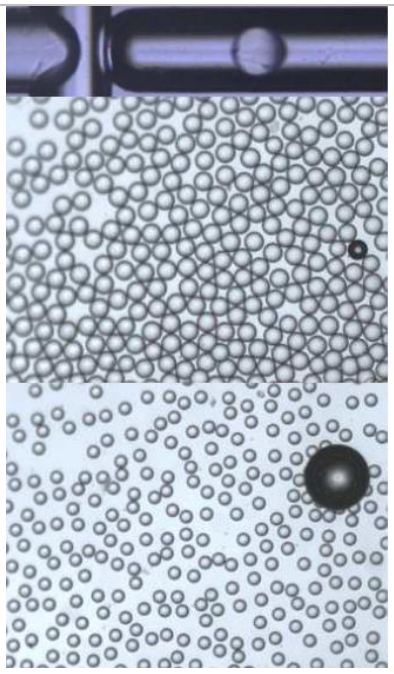
Carrier		Droplet		Junction Image	Droplet Diameter	Droplet Rate
Pressure/ mbar	Flow rate µL/min	Pressure/ mbar	Flow rate µL/min		µm	Hz
260	10	866	1.31		86 (on chip) 84 (initial size on glass slide) 40 (final size on the glass slide)	65
513	20	1104	1.31		78	87
786	30	1146	1.31		72	111
1085	40	1170	1.31		68 (on-chip) 67 (initial size on glass slide) 35 (final size on glass slide)	135

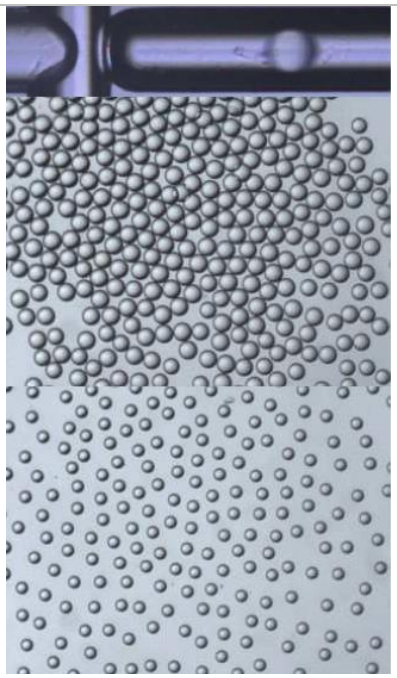
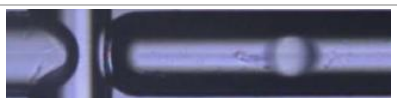
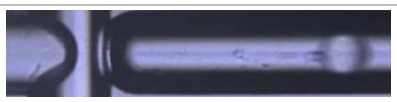
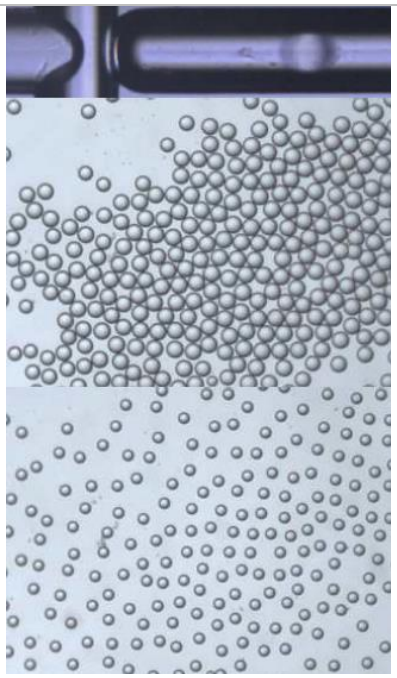
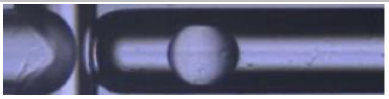
1391	50	1216	1.31		65	155
1669	60	1239	1.31		60	194
1949	70	1262	1.31		55 (on-chip) 52 (initial size on glass slide) 31 (final size on glass slide)	246
2226	80	1290	1.31		50	335
2497	90	1316	1.31		47	405
2766	100	1341	1.31		44 (on-chip) 43 (initial size on glass slide) 28 (final size on glass slide)	496
351	10	6198	11.12		-	-

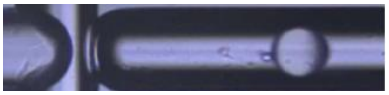
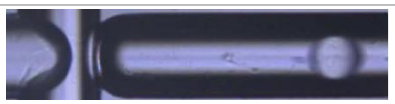
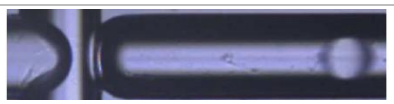
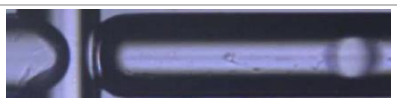
618	20	6277	11.12		92	461
872	30	6295	11.12		84	600
1143	40	6320	11.12		76	801
1426	50	6574	11.12		70	1032
1605	60	6636	11.12		66	1223
1999	70	6704	11.12		63	1410
2255	80	6707	11.12		59	1703
2522	90	6700	11.12		54	2267
2788	100	6665	11.12		50	2832
3506	125	6693	11.12		Chaotic	
4224	150	6746	11.12		Chaotic	
100	4	690	0.52		93	21
246	10	695	0.52		82	31
503	20	705	0.52		75	40
1350	50	780	0.52		62	69

1.1.4 20% PLGA solution

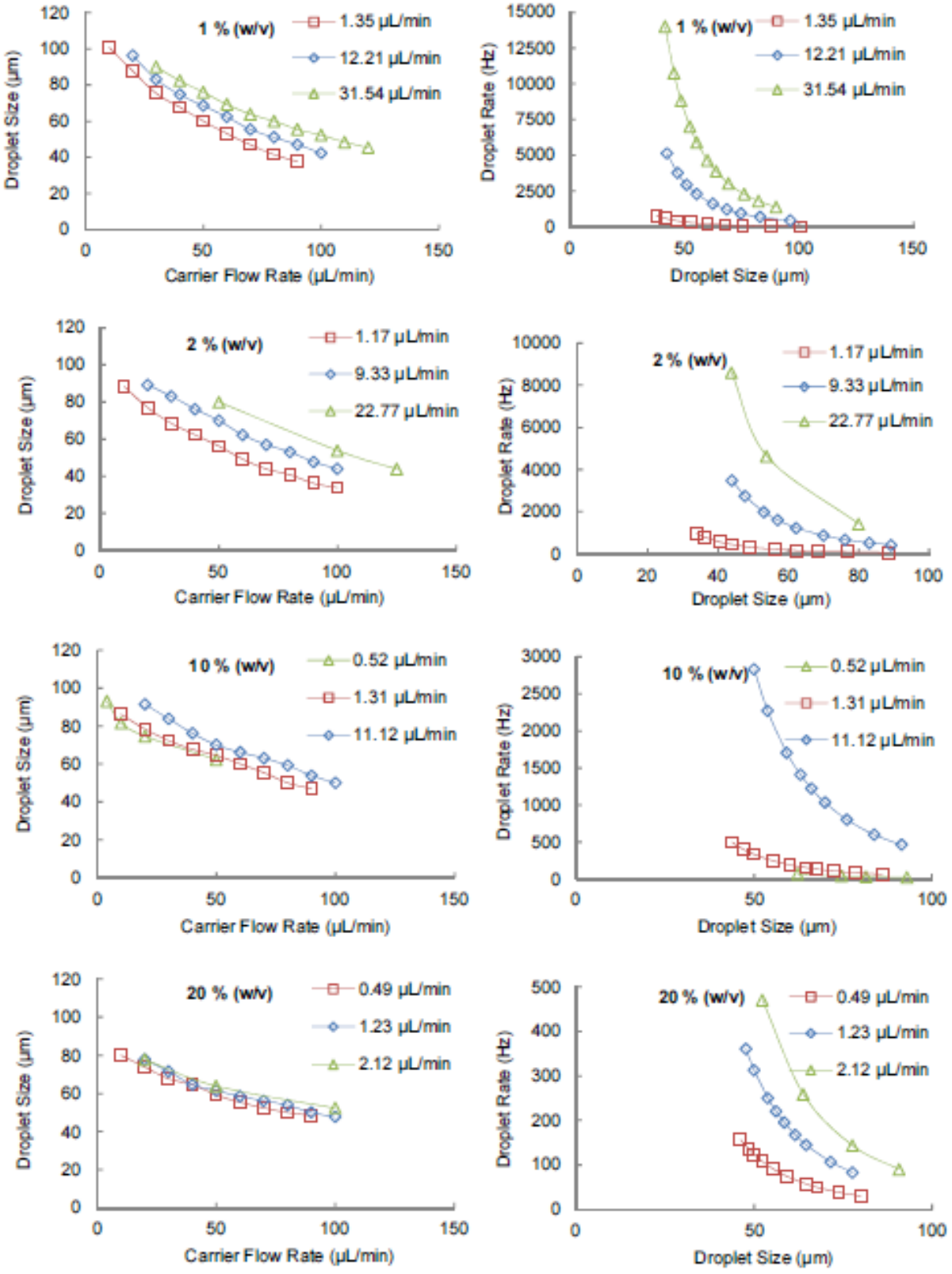
Carrier	Droplet	Junction Image	Droplet Diameter	Droplet Rate

Pressure/ mbar	Flow rate µL/min	Pressure/ mbar	Flow rate µL/min		µm	Hz
252	10	1636	0.49		80 (on-chip) 74 (initial size on glass slide) 44 (final size on glass slide)	30
531	20	1650	0.49		74	38
811	30	1766	0.49		68	50
1121	40	1860	0.49		65 (on-chip) 56 (initial size on glass slide) 39 (final size on glass slide)	57
1434	50	1955	0.49		59	74
1736	60	2069	0.49		55	91

2026	70	2093	0.49		52 (on-chip) 50 (initial size on glass slide) 37 (final size on glass slide)	108
2299	80	2206	0.49		50	124
2594	90	2236	0.49		48	136
2269	100	2555	0.49		46 (on-chip) 43 (initial size on glass slide) 35 (final size on glass slide)	157
266	10	4728	1.23		88	58
532	20	4738	1.23		78	83
817	30	4744	1.23		72	107

1130	40	4799	1.23		65	145
1430	50	4835	1.23		62	168
1732	60	4832	1.23		58	196
2025	70	4919	1.23		56	221
2296	80	4920	1.23		54	251
2582	90	4932	1.23		50	313
2888	100	4989	1.23		48	361
150	3	7391	2.12		Chaotic	
280	10	7359	2.12		91	90
538	20	7321	2.12		78	144
1435	50	7389	2.12		64	259
2888	100	7565	2.12		52	471

1.1.5 Graphical representation of results



Left: Droplet size variation with carrier flow for 3 droplet flow rates.

Right: Size and droplet rate dependence for the same for 3 droplet flow rates.

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